

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-205

PHARMACOLOGY REVIEW(S)

PHARMACOLOGIST'S REVIEW

NDA 21-205.000

Date Submitted: December 20, 1999

Date Assigned: February 7, 2000

Date Completed: February 16, 2000

Assigned Reviewer: Pritam Verma, Ph.D.

DAVDP

HFD-530

SPONSOR: Glaxo Wellcome, Inc.

Five Moore Drive

Research Triangle Park, NC 27709

INFORMATION TO SPONSOR: Yes

DRUG: Trizivir™ Tablets

(Abacavir Sulfate 300 mg/Lamivudine 150 mg/Zidovudine
300 mg tablets)

1. ZIAGEN™ (abacavir)

Dosage and administration: The recommended oral dose of ZIAGEN for adults is 300 mg twice daily in combination with other antiviral agents.

Adolescents and pediatric patients: The recommended oral dose of Ziagen for adolescents and pediatric patients 3 months to up to 16 years of age is 8 mg/kg twice daily (up to a maximum of 300 mg twice daily) in combination with other antiretroviral agents.

2. EPIVIR® (lamivudine)

Dosage and administration: Adults and adolescents (12 to 16 years): The recommended oral dose of lamivudine for adults and adolescents is 150 mg twice daily (300 mg/day) administered in combination with Retrovir (zidovudine). Dose Adjustment: It is recommended that doses of Epivir be adjusted in accordance with renal function in patients older than age 16 years. Pediatric patients: the recommended oral dose of lamivudine for 3

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months to up to 12 yr of age is 4 mg/kg (up to a maximum of 150 mg twice a day) administered in combination with Retrovir.

3. RETROVIR[®] (zidovudine)

Dosage and administration: For adults, the recommended total oral daily dose is 600 mg per day in divided doses in combination with other antiretroviral agents and 500 mg (100 mg every 4 hr while awake) or 600 mg per day in divided doses for monotherapy. Pediatric patients: the recommended dose in 3 months to 12 yr of age patients is 180 mg/m² every 6 hr, not to exceed 200 mg every 6 hr.

ROUTE OF ADMINISTRATION: Oral

RELATED INDs & NDAs: _____ 19-655; 20-977; 20-798; 20-564; 20-596; 19-655; 20-518

INDICATION: Treatment of HIV infection.

INTRODUCTION AND DRUG HISTORY:

The sponsor is developing a fixed-dosage combination formulation consisting of abacavir sulfate 300 mg, lamivudine 150 mg and zidovudine 300 mg in an oral tablet (trizivir). Trizivir has been shown to be effective antiretroviral therapy in the treatment of HIV in adults and children. Results of a bioequivalence study (AZL10001) indicate that trizivir tablet is bioequivalent relative to C_{max} and AUC to abacavir, lamivudine and retrovir when given as separate tablets. The fixed-dosage tablet is to be administered as a twice daily regimen that should offer a less complicated and more convenient dosing schedule for HIV-infected patients taking abacavir 300 mg daily, lamivudine 150 mg twice daily and zidovudine 200 mg thrice daily. Presently, the sponsor submitted a NDA requesting accelerated approval of trizivir tablets.

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TOXICOLOGY AND PHARMACOKINETICS:

Abacavir sulfate, lamivudine and zidovudine are approved drug products and have been reviewed in the division. For pharm/tox studies, please see the respective reviews.

LABEL:

On line 530, the sponsor should change the number _____ to "approximately 3700."

Starting line 544, the two sentences starting with _____ should be deleted.

CONCLUSIONS:

There are no pharm/tox issues associated with this NDA.

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Pritam S. Verma, Ph.D.
Reviewing Pharmacologist

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Concurrences:

HFD-530/WDempsey

HFD-530/JFarrelly

HFD-530/PVerma

3/15/00

S/ 3/2/00

3/7/2000

Disk:

HFD-530/JFarrelly

cc

HFD-530/NDA 21-205

HFD-340

HFD-530/PVerma

HFD-530/JMartin

HFD-530/KRao

HFD-530/LConnors

HFD-530/MTruffa

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PHARMACOLOGIST'S REVIEW

NDA 21-205

Date Submitted: September 13, 2000

Date Assigned: November 13, 2000

Date Completed: November 13, 2000

Assigned Reviewer: Pritam Verma, Ph.D.

DAVDP

HFD-530

SPONSOR: Glaxo Wellcome, Inc.
Five Moore Drive
Research Triangle Park, NC 27709

INFORMATION TO SPONSOR: No

DRUG: Trizivir™ Tablets
(Abacavir Sulfate 300 mg/Lamivudine 150 mg/Zidovudine
300 mg tablets)

1. ZIAGEN™ (abacavir)

Dosage and administration: The recommended oral dose of
ZIAGEN for adults is 300 mg twice daily in combination
with other antiviral agents.

2. EPIVIR® (lamivudine)

Dosage and administration: Adults and adolescents (12
to 16 years): The recommended oral dose of lamivudine
for adults and adolescents is 150 mg twice daily (300
mg/day) administered in combination with other
antiretroviral agents.

3. RETROVIR® (zidovudine)

Dosage and administration: For adults, the recommended
total oral daily dose is 600 mg per day in divided
doses in combination with other antiretroviral agents
and 500 mg (100 mg every 4 hr while awake) or 600 mg
per day in divided doses for monotherapy.

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ROUTE OF ADMINISTRATION: Oral

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INDICATION: Treatment of HIV infection.

INTRODUCTION AND DRUG HISTORY:

The sponsor is developing a fixed-dosage combination formulation consisting of abacavir sulfate 300 mg, lamivudine 150 mg and zidovudine 300 mg in an oral tablet (trizivir). Trizivir has been shown to be effective antiretroviral therapy in the treatment of HIV. Results of a bioequivalence study (AZL10001) indicate that trizivir tablets are bioequivalent relative to Cmax and AUC to abacavir, lamivudine and retrovir when given as separate tablets. The fixed-dosage tablet is to be administered as a twice daily regimen that should offer a less complicated and more convenient dosing schedule for HIV-infected patients taking abacavir 300 mg daily, lamivudine 150 mg twice daily and zidovudine 200 mg thrice daily. Presently, the sponsor submitted an Information Amendment: Complete Response to Approval letter-Label.

TOXICOLOGY:

LABEL:

The label has been reviewed and there are no issues associated with the label.

CONCLUSIONS:

There are no pharm/tox issues associated with the label.

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/S/

Pritam S. Verma, Ph.D.
Reviewing Pharmacologist

Concurrences:

HFD-530/WDempsey

HFD-530/JFarrelly

HFD-530/PVerma

/S/ 11/13/02
11/13/2002**Disk:**

HFD-530/JFarrelly

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HFD-530/NDA 21-205

HFD-340

HFD-530/PVerma

HFD-530/LMishra

HFD-530/KRao

HFD-530/TCvetkovich

HFD-530/MTruffa

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